Rising to the challenge: Designing, implementing, and reporting exercise oncology trials in understudied populations

Running title: Exercise oncology trial design and reporting

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Abstract (50 words unstructured)

Exercise can improve cancer-related fatigue, quality of life and physical fitness, but is understudied in less common cancers such as multiple myeloma. Studying less common cancers and the adoption of novel study designs and open-science practices would improve the generalisability, transparency, rigour, credibility and reproducibility of exercise oncology research.

Exercise is an effective therapy for cancer-related fatigue[1] and improved quality of life and physical fitness in patients with cancer.[2] Most of this evidence, however, is in breast and prostate cancer populations.[2] Multiple myeloma (MM), a hematological cancer associated with fatigue, muscle atrophy, reduced physical function, and poor quality of life, is a population that could benefit from exercise rehabilitation.[3] However, there is limited available evidence for the safety, feasibility, and efficacy of exercise in this population.[3] A primary barrier in implementing physical rehabilitation is the challenge imposed by the osteolytic bone lesions present in the majority of MM patients—with over half of patients experiencing pathological fracture or spinal cord compression.[4]

A recently published exercise guideline recommended selection of exercises that reduce load in areas with lesions in patients with metastatic bone disease.[2] In MM, this approach is difficult to implement due to the extensive presence of osteolytic lesions throughout the body. The International Bone Metastases Exercise Working Group was recently established to develop guidelines that will provide further exercise guidance for patients with metastatic bone disease including recommendations for MM. An exercise guidance document is currently under development, with publication expected in 2020.

Given the increased risks and challenges of implementation of exercise in this cancer population, Koutoukidis et al. are to be commended on their study focussed on MM in this issue. The authors investigated the effects of a 6-month combined hospital-based supervised and home-based unsupervised aerobic and resistance exercise training program for MM survivors who had completed their initial treatment.[5] Importantly, no exercise-related fractures or adverse events were reported among the 51 patients who participated in the exercise arm.

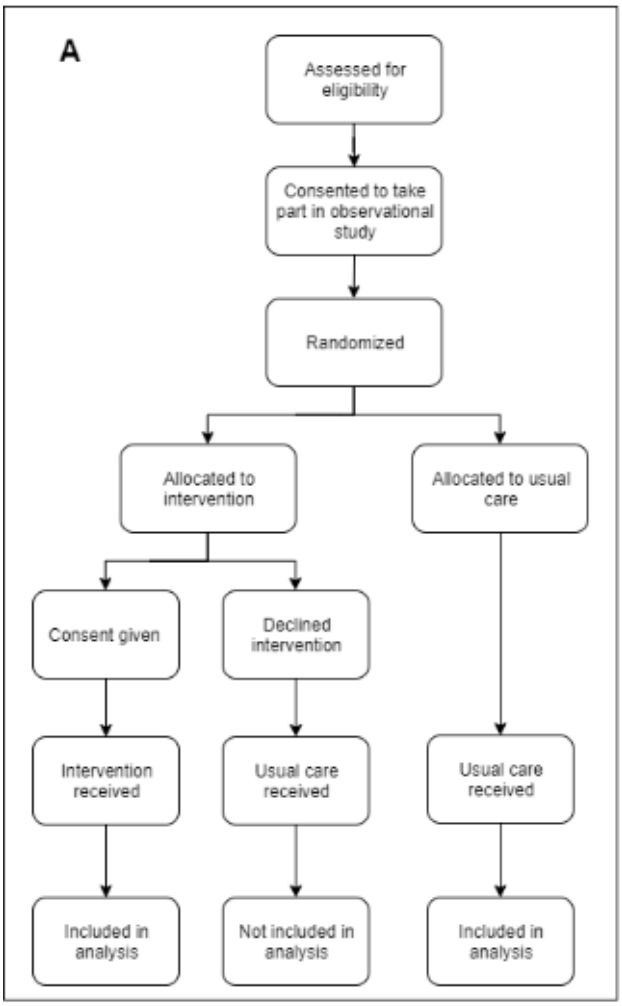
In lieu of a traditional RCT design, the authors implemented an adapted-Zelen design (more commonly known as a 'Trials within Cohorts' (TwiC) design; Figure 1A). Pragmatic trial designs, such as Zelen and TwiC approaches are proposed to overcome control group contamination and study generalizability issues. In Zelen designs, consent is sought after randomization either from patients who have been allocated to the intervention (single consent, Figure 1B) or from patients in both intervention and usual care groups (double consent, Figure 1C). While the aim is to reduce disappointment bias when patients are not allocated to their preferred treatment, remove subjective recruitment bias, and minimize control group contamination,[6] the ethics of Zelen designs have been questioned due to randomization without consent and withholding treatment option information.[7]

In comparison, TwiC designs seek consent first from patients invited to participate in an observational trial, and secondly from patients within the cohort population if they are randomly allocated to an intervention (Figure 1A, 1D). TwiC trials also aim to increase external validity by retaining characteristics of normal clinical practice.[7] However, as observed by Koutoukidis et al. and a previous exercise oncology trial,[8] TwiC studies in exercise oncology have reported high refusal rates of the intervention (43 and 48%, respectively),[5,8] resulting in potentially underpowered analyses and dilution of intervention effects. This could have contributed to the lack of effect of the exercise intervention on fatigue, physical or emotional functioning, anxiety, depression, or physical activity levels in the trial of Koutoukidis et al.[5] This suggests that more

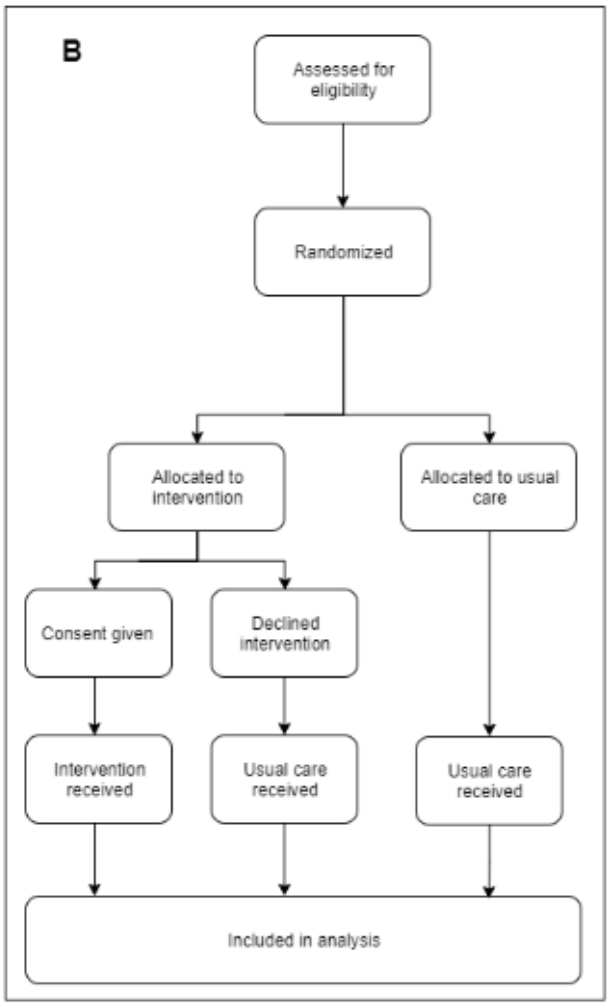
education on the potential benefits of exercise may be required to enhance patient interest and the utility of these novel study designs.

While we appreciate the use of a novel study design and focus on an understudied, challenging population by Koutoukidis et al., the field of exercise oncology in general will benefit from further widespread adoption of a number of science reform practices. Recent Cochrane Collaboration systematic reviews of exercise oncology studies report widespread practices that reduce credibility and reproducibility of results, including poor reporting standards, lack of prospective and/or detailed registration, low adherence to principles of exercise training, lack of blinding of outcome assessors and statisticians, and underpowered statistical analyses.[9,10]

We believe that the adoption of a number of open science practices would improve the rigor, transparency, credibility, and reproducibility of exercise oncology research. For example, poor reporting practices can be relatively easily improved through diligent adherence to standard reporting guidelines (i.e., CONSORT-NPT, CERT) in the study design and reporting stages. Similarly, issues of exercise prescription design can be addressed through consideration of exercise training principles[11] and reporting guidelines (e.g., CERT). Adherence to and adoption of these guidelines requires a change in researcher behavior and editorial policy, as well as editorial and peer reviewer monitoring and scrutiny.



Koutoukidis et al. (2020)
Trials within Cohorts Design



Single consent Zelen design

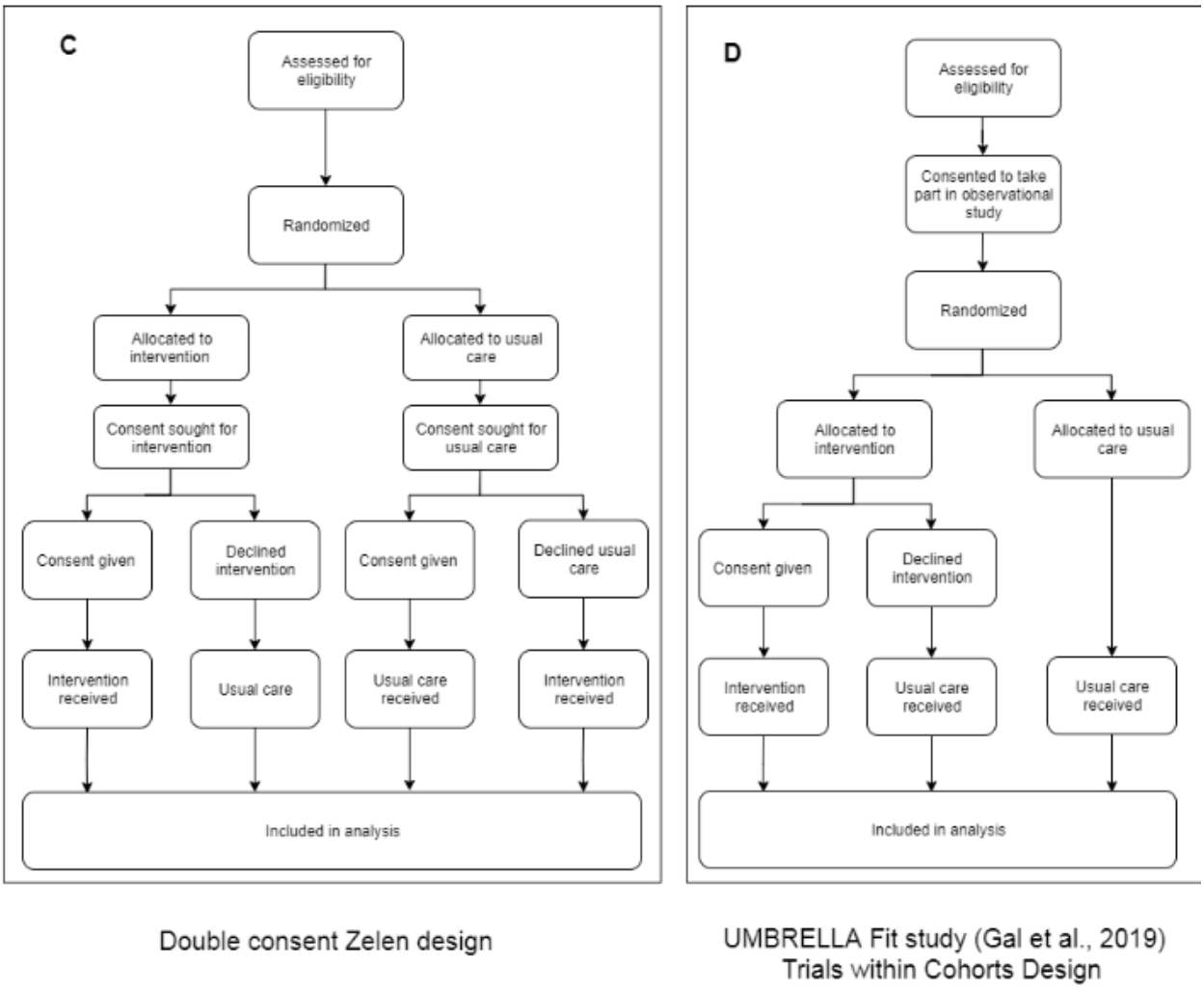


Fig. 1 Diagrams of pragmatic study designs. A) Trials within cohort design used in Koutoukidis et al.;[5] B) single-consent Zelen design; C) double-consent Zelen design; D) trials within cohort design used in Gal et al.[8]

Prospective, detailed, and transparent pre-registration of trials can help solve a number of issues in exercise oncology. Preregistration helps to distinguish between confirmatory and exploratory research by making it clear which decisions (e.g., selection of primary outcomes and their analyses) were planned *a priori* (confirmatory) and which were made *post hoc* (exploratory).[12] Preregistration can also be used to detect questionable research practices such as selective outcome reporting, *p*-hacking, and Hypothesizing After the Results are Known (HARKing).[12] Lastly, preregistration can elucidate the prevalence and impact of publication bias and positive reporting bias by investigating how many and which planned trials are completed and published.

A promising and novel publishing format, Registered Reports, involves peer review and acceptance (for publication in principle) of preregistered proposals prior to data collection. A key benefit is that studies are judged on relevance and importance of the research question and the robustness and rigor of the trial design, and not on the study's results. Registered Reports can

also help to solve the problem of underpowered analyses by requiring confirmatory studies to be adequately powered. However, the challenge of acquiring the larger samples required to achieve sufficient statistical power and move exercise oncology beyond phase II to phase III trials remains. One solution to this problem is to encourage greater multi-centre collaboration. Indeed, to establish the benefits of exercise in patients with less common cancers such as MM, national or international collaborations are likely required.

In summary, to fully elucidate the effectiveness of exercise in the management of patients with cancer, we recommend the use of novel, pragmatic research designs, inclusion of less common cancer types, and adoption of open science practices.

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